Original Article

A comparison of heparin/warfarin and enoxaparin thromboprophylaxis in spinal cord injury: the Sheffield experience

P Thumbikat^{*1}, PM Poonnoose¹, P Balasubrahmaniam¹, G Ravichandran¹ and MR McClelland¹

¹Princess Royal Spinal Injuries Unit, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK

Objectives: To compare the safety and effectiveness of two different thromboprophylactic protocols in the management of patients with spinal cord injury – one using heparin/warfarin and the other using enoxaparin.

Study design: Retrospective.

Setting: Princess Royal Spinal Injuries Unit, Sheffield, UK.

Methods: Retrospective review of two cohorts of patients with acute spinal injury admitted to a supra-regional spinal injuries centre and treated with different pharmacological agents. One group received heparin/warfarin in combination with antiembolism stockings and mechanical measures for thromboprophylaxis whereas the second group received enoxaparin in combination with the other measures. Patients who developed clinical symptoms suggestive of deep vein thrombosis or pulmonary embolism were investigated as appropriate.

Results: Four of the 101 patients on heparin/warfarin developed symptoms of venous thromboembolism compared to 13 of the 72 who were on enoxaparin. Of the 13, three had been on 40 mg of enoxaparin daily and 10 on 20 mg enoxaparin daily. Six patients on enoxaparin and one patient on warfarin developed thromboembolic complications after they had been mobilised and the anticoagulant discontinued. Eight patients on warfarin prophylaxis and three patients on enoxaparin developed haemorrhagic complications necessitating cessation of therapy.

Conclusion: This study suggests that the traditional protocol of warfarin/heparin for thromboprophylaxis in spinal cord injury patients remains a safer option than enoxaparin.

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Keywords: spinal cord injury; thromboembolism; warfarin; enoxaparin; deep vein thrombosis; pulmonary embolism

Introduction

Deep vein thrombosis (DVT) and Pulmonary embolism (PE) are medical complications not uncommonly seen following acute spinal cord injury. Different treatment modalities have been advocated and tried in the spinal cord injured population in an attempt to prevent DVT and PE with varying degrees of success. Outcomes have been better when treatment protocols used a combination of measures that targeted various risk factors individually.^{1,2}

Different protocols using oral anticoagulants, heparin, low molecular weight heparins, vena caval filters and antithrombotic stockings have been demonstrated to provide effective prophylaxis in patients with spinal cord injuries.³ Low molecular weight heparins

(LMWH) were introduced in the later half of the eighties. These are fractionated portions of the heparin molecule that exert specific antithrombotic effects with longer duration of action. The use of LMWH is associated with lesser incidence of thrombocytopenic complications and more predictable bioavailability.

Until 1998 patients admitted to the Princess Royal Spinal Injuries Unit, Sheffield (PRSIU) with acute traumatic spinal cord injury received a combination of subcutaneous heparin and warfarin for thromboprophylaxis. In addition antiembolism stockings, frequent passive movements of the lower limbs and two hourly changes of position were employed in all patients.

In 1998, influenced by the generally positive reports in peer-reviewed literature^{3–5} on the use of LMWH in spinal cord injury (SCI) patients the thromboprophylactic protocol in the unit was changed to one that used enoxaparin as the pharmacologic agent instead of

*Correspondence: P Thumbikat, Princess Royal Spinal Injuries Unit, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK

heparin and warfarin. No changes in the use of stockings and passive movements were introduced.

We describe our experiences with both protocols.

Material and methods

This is a retrospective study comparing the efficacy of thromboprophylactic measures in two groups of patients admitted to Princess Royal Spinal Injuries Unit with sensory motor paralysis following a spinal cord injury. The first group (group 1) comprised of all acute traumatic spinal cord injury admissions to the unit between January 1990 and February 1992. All consecutive acute traumatic admissions to the unit between January 1999 and June 2000 constituted the second group (group 2).

Group 1 received a combination of heparin followed by warfarin for thromboprophylaxis. Subcutaneous heparin was administered soon after admission in a dose of 5000 units twice daily and warfarin commenced as soon as the patient was able to tolerate oral fluids. Heparin was discontinued once target INR levels of 2.0 had been achieved. Group 2 received enoxaparin as the thromboprophylactic agent. This was started on the day of admission. The second group was further subdivided into those who received 20 mg of enoxaparin (Group 2A) as the thromboprophylactic agent (Clexane, Rhone Poulenc Rorer) and those who received 40 mg of enoxaparin (Group 2B). Anticoagulation was discontinued in both groups only after the patients had been mobile in a wheelchair for several hours each day undergoing physical rehabilitation.

The patients were assessed daily and further investigations undertaken if there were clinical grounds to suspect a venous thromboembolic episode. For the purpose of this study, a diagnosis of DVT was made if it had been proven by Doppler scan and a PE was said to have occurred if it had been documented by a ventilation perfusion mismatch on a ventilation perfusion (V/Q) scan. A suspected PE was deemed to have occurred if V/Q scans were inconclusive, but clinical symptomatology had been sufficient enough to start full therapeutic anticoagulant treatment.

We excluded those patients who had been on anticoagulation for more than 1 year before injury, non-traumatic acute admissions and non-acute admissions. We also excluded those patients whose medical records did not contain details of their anticoagulation therapy prior to the transfer to the Spinal Injuries Unit.

Patient records were reviewed for documentation of DVT, PE, complications and duration of anticoagulation, results of Doppler studies, V/Q scans and unexplained decrease in haemoglobin and platelet levels. Details of other relevant contributory factors such as associated injuries, surgical intervention, level of injury and anticoagulation prior to admission to Princess Royal Spinal Injuries Unit were also reviewed.

Results

We reviewed 152 and 87 records from 1990–1991 and 1999–2000 respectively. One hundred and one and 72 patients respectively satisfied the inclusion criteria. The patient characteristics are shown in Table 1. Men outnumbered women by a large margin in both groups. In group 1, 50.5% of patients sustained complete injuries compared to 38.9% in group 2. Chest injuries and long bone injuries were the commonest associated injuries. Spinal stabilisation was undertaken in 55.6% of patients in 1999–2000 compared to only 20.6% of

Table 1 Patient characteristics and incidence of VT

	1990–1991 (n = 101)	1999–2000 (n = 72)
Sex		
Males	1 (77)	12 (52)
Females	3 (24)	1 (20)
VT	4 (101)	13 (72)
DVT	2	5
PE	1	4
DVT and PE	0	1
Suspected PE	1	3
Age		
10–30	1 (55)	3 (25)
31–40	0 (21)	4 (16)
41–50	2 (9)	3 (8)
51–60	0 (6)	1 (6)
> 60	1 (10)	2 (17)
Level		
Cervical	2 (36)	7 (38)
Thoracic	2 (46)	5 (24)
Lumbar	0 (19)	1 (10)
Complete	3 (51)	3 (28)
Incomplete	1 (50)	10 (44)
Associated injuries		
Head	0 (6)	1 (7)
Pelvis/Limb	1 (18)	1 (4)
Chest	1 (13)	3 (16)
Spinal stabilisation	2 (21)	6 (40)
No spinal stabilisation	2 (80)	7 (32)
Mortality	0	0
Premobilisation		
DVT	2	3
PE	1	4
Post mobilisation		
DVT	0	5
PE	1	1
Complications	8	3
Gastric Bleed	3	1
Bleeding PR	4	0
Haematoma Limbs	1	0
Pressure sore bleeding	0	0
Haematuria	0	2

Figures in parentheses indicate sample size for each group

patients in 1990–1991. The average time to transfer to the spinal injuries unit from the admitting hospital was just over 12 days in both groups (range 0–80).

In 1990–1991, prior to transfer to Princess Royal Spinal Injuries Unit, all patients had received heparin prophylaxis. By 1999, the acute hospitals in the region had switched to the use of different low molecular weight fractions of heparin, which were often what patients in the second group received prior to transfer to spinal injuries unit (Table 2).

The average period of anticoagulation in the 1990–1991 was 57 days (range 6–118 days). These patients were mobilised at an average of 57.3 days (range 8 to 111).

Of the 72 patients in group 2, 40 patients were treated with 20 mg of enoxaparin (group 2A) and 32 with 40 mg of enoxaparin (group 2B). The average period of anticoagulation in 1999–2000 was 52 days and the average period to mobilisation was 59.6 days (range 25–152).

Four patients (4%) in group 1 and 13 patients (18%) in group 2 developed venous thromboembolic (VT) episodes. Ten patients in group 2A (25%) and three patients in group 2B (9.4%) developed DVT/PE (see Table 2). In group 1, one of the thrombotic events occurred *post mobilisation*. Six of the 13 thrombotic events in group 2 occurred after the patients had been mobilised and anticoagulation stopped.

Two periods of peak incidence of venous thromboembolism were noticed in both groups – the first at days 20 to 30 following the injury and the second at days 90–100 following injury (Figure 1).

Eight of the 101 patients in group 1 and three in group 2 developed anticoagulant related complications. The three patients in group 2 had been on the 20 mg enoxaparin dose. In this study no patient suffered a fall in haemoglobin or platelet levels necessitating cessation of anticoagulant therapy.

The data was statistically analysed using SPSS for windows (SPSS for Windows software package Version 10.1.0; ©SPSS, Inc) package. Binary logistic regression analysis was done using age, sex, anticoagulant used, duration of anticoagulation, spinal stabilisation and associated injuries as the variables and venous thromboembolism episode as the outcome. The only significant variable noticed was the anticoagulant used ($P=0.009$, 95% confidence intervals 1.5–18.5, odds ratio=5.3).

Discussion

Prevention of DVT using pharmacological agents has been in vogue since the seventies. The drugs and the protocols employed in the spinal injured population have evolved over a period of time and have generally reflected the prophylactic regimens used in contemporary surgical practice at the time.

Early studies evaluated the benefit of thromboprophylactic measures.⁶ Heparin^{7,8} and Phenindione⁹ were found to be effective thromboprophylactic agents. In a separate study, heparin was found to be more effective than sintrom.¹⁰ However, other studies that looked at the role of heparin in spinal cord injured population found it to be no more effective than a placebo.¹¹ The addition of mechanical thromboprophylactic measures enhanced the protective effect.¹²

A number of authors have reported on the advantages and efficacy of LMWH since the early 90s. Green used LMWH in a dose of 3500 anti Xa units and reported no VT episodes in 20 patients.³ VT episodes occurred in none of the 105 patients treated with enoxaparin in a preliminary report by Harris, Chen and Green.⁵ No study to date has directly compared the use of LMWH to warfarin in SCI patients.

Figure 1 Temporal distribution of thromboembolic events

Table 2 Composite table showing the anticoagulation protocol used prior to transfer to SIU in Group 2 patients

Group 2	Same	Anticoagulation protocol used prior to transfer to PRSIU			Not known
		Other LMWH	Heparin/warfarin	Combination	
Group 2A	6 (19)	1 (6)	1 (1)	0 (0)	2 (14)
Clexane 20 mg (40)					
Group 2B	1 (14)	0 (10)	0 (0)	1 (1)	1 (7)
Enoxaparin 40 mg (32)					

Bold figures represent incidence of venous thromboembolic episodes in the subgroup and the figures in parentheses represent the sample size for the subgroup

A comparison of various protocols is fraught with difficulty as the methods employed to detect DVT varied widely. Studies that used radiolabelled fibrinogen and venography were more sensitive and had high pick up rates. Clinical incidence of DVT rose from 17% to 100% when the above techniques were employed.^{13–15} The relevance of subclinical DVT remains uncertain.

The present study compared a population of patients who were mobilised some 6 to 8 weeks following the injury and who remained in the unit for several weeks thereafter undergoing physical rehabilitation. Patients who were prophylactically treated with the traditional heparin/warfarin regime had a lesser incidence of VT episodes than patients who were treated with enoxaparin. This was true for both DVT and PE. When enoxaparin was first introduced in the unit, a thromboprophylactic dose equivalent to 10 000 units of calcium heparin was used, the latter being the dose in use at the time. However after a few months, anecdotal evidence and clinical impression suggested an increasing incidence of VT. Subsequently, a multidisciplinary meeting suggested an increase to 40 mg of enoxaparin, the maximum recommended by the British National Formulary for thromboprophylaxis. The higher dose of enoxaparin offered greater protection against VT than 20 mg, though it was not as effective as warfarin. Increasing the dose did not alter the side effect profile. All the patients who experienced haemorrhagic complications while on enoxaparin were on the 20 mg dose.

The incidence of haemorrhagic complications was higher with warfarin than enoxaparin. This is in sharp contrast to a study on patients who underwent knee arthroplasty, where enoxaparin produced more haemorrhagic complications.¹⁶ Two other studies that looked at enoxaparin reported a low incidence of haemorrhagic complications^{5,17} (one patient each in sample sizes of 60 and 276 patients respectively).

Although more patients in the 1999 group underwent spinal fixation, it did not make any difference to the incidence of venous thromboembolic complications. Similarly, the severity of associated injuries did not favour an increase in the incidence of VT. Those who had sustained cervical injuries appeared to be more prone to VT than those with lower injuries.

Two periods of greater susceptibility to VT were noticed in both groups. The first was at days 20 to 30, a little later than what has been classically described as the period of greatest risk. The second peak was beyond 90 days, during the period of physical rehabilitation. The reason for that is not clear. It is likely that preformed sub clinical clots in the deep veins detach during the period of rehabilitation. This was more of a problem with the enoxaparin group, 50% of the events having occurred post mobilisation and discontinuation of anticoagulation. Our findings are in agreement with a recent study from Glasgow where five of the eight patients who experienced a VT

episode did so after discontinuation of anticoagulation.¹⁷

Previous studies have looked at thromboprophylaxis during the acute management of the paralysed patient and the periods of follow-up have tended to be short. In the UK, patients are confined to bed for a few weeks following spinal injury before mobilisation and commencement of rehabilitation. The role of this period of recumbency in the genesis of VT in patients appropriately anticoagulated is uncertain. Unlike many North American studies,^{3–5,12} the patients in our study were followed up for a longer period of time by the same rehabilitation team, thus offering an opportunity to evaluate the true incidence of VT. The follow-up periods in many of these studies^{3–5,12} were variable, probably reflecting local medical insurance practices. A dose of 60 mg of enoxaparin was used in the American studies, which may be a reason for the reduced incidence of VT. These studies have also not reported on the second peak of thromboembolic events seen in our study.

The incidence of VT following cessation of anticoagulation is also in marked contrast to our experience with long term SCI patients admitted with intercurrent problems such as pressure sores and urological problems. Although many of these patients are confined to bed for long periods without prophylactic anticoagulation, clinically significant VT does not seem to be a problem in these patients.

We conclude that the traditional anticoagulation protocol using heparin and warfarin still remains a safe option despite the introduction of newer low molecular weight derivatives of heparin. The duration that patients need to be on prophylactic anticoagulation remains to be satisfactorily resolved.

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